AN EFFICIENT SYNTHESIS OF 2-AROYL-1H-INDOLES

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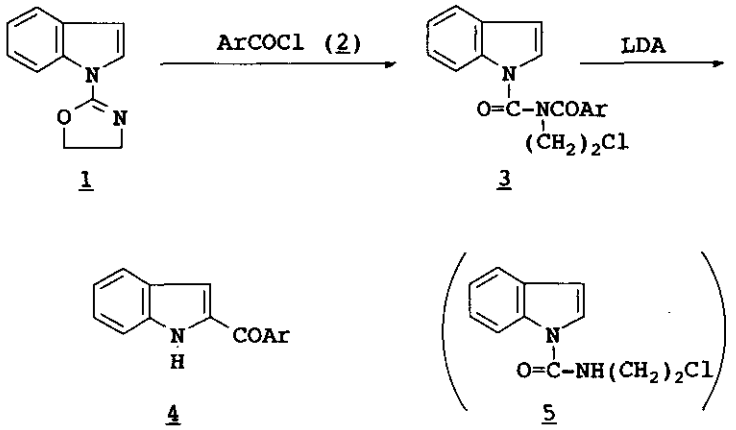
Abstract —— 2-Aroyl-1H-indoles were directly obtained by the reaction of 1-(N-aroylcarbamoyl)indoles, prepared from 1-(2-oxazolinyl)indole and aroyl chlorides, with LDA.

Various procedures for regioselective functionalization of an indole ring at the 2-position have been well documented.[1] It was demonstrated, very recently, that the N-tert-butylcarbamoyl group on the 1-position of indole played a crucial role as a removable and directing group for the synthesis of 2-substituted 1H-indole derivatives.[2] The results prompt us to report an effective procedure for the preparation of 2-aroyl-1H-indoles (4), which are potential synthetic intermediates for a variety of biologically active compounds, from 1-(2-oxazolinyl)indole (1).[3]

The compound (1) (1.0 mmol) was heated with an aroyl chloride (2, 1.05 mmol) in benzene for 10-12 h under argon atmosphere. After concentration of the reaction mixture in vacuo, the residue was purified by flash chromatography (silica gel-benzene) to give 1-(N-aroylcarbamoyl)indole (3)[4] as an oil in excellent yield. The solution of 3 (1.0 mmol) in tetrahydrofuran (THF) was treated with lithium diisopropylamide (LDA, 1.5 M in cyclohexane, 1.1 equiv.) at -80°C for 30 min , then allowed to stand at room temperature

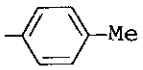
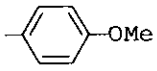
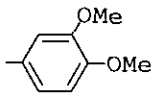
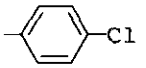
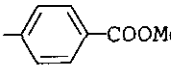
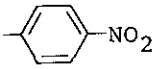


1 3 4 5

overnight with stirring under argon. The reaction mixture was treated with a few drops of sat. aq. NH_4Cl, and dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel - CH_2Cl_2 : hexane = 3 : 1) to afford 2-aroyl-1H-indole (4). 2-Lithiation followed by intramolecular acyl migration and simultaneous removal of 1-substituent of 3 were presumably involved in the reaction. Results are listed in Table.

It would be interest to note that the reaction of 3 (Ar = 4-NO_2-C_6H_4-), prepared from 1 and 2 (Ar = 4-NO_2-C_6H_4-) in quantitative yield, with LDA under the same conditions described above, gave dearoylated compound (5)[5] as a major product (25% yield) together with only 7% yield of 4 (Ar = 4-NO_2- C_6H_4), suggesting that the formation of 4 from 3 might be dependent on the nucleophilic reactivity of aroyl carbonyl in the latter. Ready deprotection on the 1-position of indole, occurred in the reaction of 3 to 4, might be attributable to electronic effects of 2-aroyl substituent introduced.[2] The present procedure for regiospecific 2-aroylation of indole would be applicable to the synthesis of highly functionalized indoles of biological interest under mild reaction conditions. Further studies to develop the utilities of this method are now in progress.

Table. 1-(N-Aroylcarbamoyl)indoles (3) and 2-aroyl-1H-indoles (4)

Run		Yield(%) of 3	Yield(%) of 4	mp(°C) of 4*	lit. mp(°C) of 4
1		95	73	151-2	149-50[6]
2		84	61	186-7	185-6[7]
3		86	69	191-2	190-1[6]
4		86	60	126-7[8]	——
5		quant.	52	196-7	203-4[9] 196-8[10]
6		quant.	34	193-4[11]	——
7		quant.	7	208-9[12]	——

* Recrystallized fron i-Pr_2O/AcOEt

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8. 4 [Ar=3,4-$(MeO)_2$-C_6H_3] : ^{1}H-Nmr[400 MHz, $CDCl_3$/TMS, δ, J(Hz)]† : 3.98 (3H, s), 3.99(3H, s), 6.98(1H, d, J=8.8), 7.17(1H, t, J=7.6), 7.17(1H, s), 7.37(1H, t, J=7.6), 7.48(1H, d, J=8.3), 7.56(1H, s), 7.73(1H, d, J=8.3), 7.74(1H, d, J=8.8), 9.33(1H, br s) : Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found : C, 72.75; H, 5.40; N, 4.85.

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11. 4 (Ar=4-MeOCO-C_6H_4) : ^{1}H-Nmr[400 MHz, $CDCl_3$/TMS, δ, J(Hz)]† : 4.00(3H, s), 7.15(1H, s), 7.18(1H, t, J=7.6), 7.40(1H, t, J=7.6), 7.49(1H, d, J=8.3), 7.73(1H, d, J=8.3), 8.03(2H, d, J=8.3), 8.20(2H, d, J=8.3), 9.36(1H, br s) : Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found : C, 73.30; H, 4.68; N, 4.94.

12. 4 (Ar=4-NO_2-C_6H_4) : ^{1}H-Nmr[400 MHz, $CDCl_3$/TMS, δ, J(Hz)]† : 7.14(1H, s), 7.20(1H, t, J=7.6), 7.43(1H, t, J=7.6), 7.50(1H, d, J=8.3), 7.73 (1H, d, J=8.3), 8.12(2H, d, J=8.8), 8.39(2H, d, J=8.8), 9.26(1H, br s) : Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.76; N, 10.52. Found : C, 67.45; H, 3.68; N, 10.37.

† Couplings with J-value less than 2 Hz were omitted.

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